

We claim.

1. An inhibitor of catalytically active memapsin 2 which binds to the active site of the memapsin 2 defined by the presence of two catalytic aspartic residues and substrate binding cleft.

5 2. The inhibitor of claim 1 comprising an isostere of the active site of memapsin 2.

3. The inhibitor of claim 2 comprising a molecule having the general form  $X-L_4-P_4-L_3-P_3-L_2-P_2-L_1-P_1-L_0-P_1'-L_1'-P_2'-L_2'-P_3'-L_3'-P_4'-L_4'-Y$ , wherein  $P_x$  represent the substrate specificity position relative to the  
10 cleavage site which is represented by an  $-L_0-$ , and  $L_x$  represent the linking regions between each substrate specificity position,  $P_x$ , and  
wherein  $L_0$  is a non-hydrolyzable bond and  $P_1'$  is  $-R_1CR_3-$ , wherein  $R_1$  is a group smaller than  $CH_2OH$  (side chain of serine), and at least two other  $P$  positions are a hydrophobic group.

15 4. The inhibitor of claim 3 which is OM99-1.

5. The inhibitor of claim 3 which is OM99-2.

6. The inhibitor of claim 3 having the structure of Figure 11.

7. The inhibitor of claim 3 having the structure of Figure 12.

8. The inhibitor of claim 3 having the structure of Figure 13.

20 9. The inhibitor of claim 3 having the structure of Figure 14.

10. The inhibitor of claim 1 having an  $K_i$  of less than or equal to  $10^{-7}$  M.

11. The inhibitor of claim 1 which binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2.

25 12. The inhibitor of claim 11 having a  $K_i$  of less than or equal to  $10^{-6}$  M.

13. The inhibitor of claim 11 having a  $K_i$  of less than or equal to 2 nM.

30 14. The inhibitor of claim 13 having a  $K_i$  of less than or equal to 1 nM.

15. The inhibitor of claim 11 having a root mean square difference of less than or equal to 0.5 Å for the side chain and backbone atoms for amino acids 18-379 of memapsin 2.

16. The inhibitor of claim 1 which is permeable to the blood brain  
5 barrier.

17. The inhibitor of claim 1 which blocks cleavage by memapsin 2 under physiological conditions.

18. The inhibitor of claim 1 which is a non-amino acid small molecule.

19. The inhibitor of claim 18 having a molecular weight of less than  
10 800 Daltons.

20. A method of synthesis of a Leu\*Ala dipeptide isostere.

21. A method for treating a patient to decrease the likelihood of  
15 developing or the progression of Alzheimer's disease comprising administering to the individual an effective amount of an inhibitor of memapsin 2 having an  $K_i$  of less than or equal to  $10^{-7}$  M or which binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2.

22. The method of claim 21 wherein the inhibitor is administered orally.

23. The method of claim 21 wherein the inhibitor blocks cleavage of  
20 APP.

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